

Patent
Attorney Docket No. 65731-76121

AMENDMENTS TO THE SPECIFICATION:

Please amend paragraph 0001 of the application as follows:

[0001] The von Hippel-Lindau (VHL) disease is caused by germ line mutations of the VHL susceptibility gene. These mutations lead to the development of a variety of tumors ~~inline-numberinglineincluding~~ including clear cell carcinomas of the kidney, pheochromocytomas and vascular tumors of the central nervous system and retina (Maher, E. R. et al., Medicine, 76:381-391, 1997; Kaelin, W. G. et al., Trends Genet., 14:423-426, 1998). Functional inactivation of both VHL alleles has been documented in a majority of sporadic clear cell renal carcinomas (Gnarra, J. R. et al., Nat. Genet., 7:85-90, 1994). Furthermore, reintroduction of a wild-type but not mutant VHL cDNA into VHL (-/-) renal carcinoma cells suppresses their ability to form tumors in nude mouse xenograft assays (Iliopoulos, O. et al., Nat. Med., 1:822-826, 1995; Gnarra, J. R. et al., Proc. Natl. Acad. Sci., 93:10589-10594, 1996). VHL-associated neoplasms are typically hypervascular and overproduce angiogenic factors such as vascular endothelial growth factor (VEGF) (Takahashi, A. et al., Cancer Res., 54:4233-4237, 1994; Witzigmann-Voos, S. and Plate, K. H., Histol. Histopathol., 11:1049-1061, 1996). Moreover, it has been shown that hypoxia-inducible inducible mRNAs, including VEGF mRNA, are constitutively expressed under normoxic conditions in VHL-deficient cells (Gnarra, J. R. et al., Proc. Natl. Acad. Sci., 93:10589-10594, 1996; Iliopoulos, O. et al., Nat. Med., 1:822-826, 1995; Siemeister, G. et al., Cancer Res., 56:2299-2301, 1996). Reintroduction of VHL into VHL (-/-) renal carcinoma cells indicates that it functions as a negative regulator of VEGF mRNA levels by either post-transcriptional mechanisms (Gnarra, J. R. et al., Proc. Natl. Acad. Sci., 93:10589-10594, 1996; Iliopoulos, O. et al., Nat. Med., 1:822-826, 1995; Siemeister, G. et al., Cancer Res., 56:2299-2301, 1996) and/or transcriptional mechanisms (Mukhopadhyay, D. et al., Mol. Cell. Biol., 17:5629-5639, 1997).